Gastroenterology 2022;163:118–136

GUIDELINES

AGA Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome With Constipation

Lin Chang,[1,*] **Shahnaz Sultan**,[2,3,*] Anthony Lembo,[4] G. Nicholas Verne,[5] Walter Smalley,[6] and Joel J. Heidelbaugh[7]

[1]*Vatche and Tamar Manoukian Division of Digestive Diseases, David Geffen School of Medicine at University of California-Los Angeles, Los Angeles, California;* [2]*Division of Gastroenterology, Hepatology, and Nutrition, University of Minnesota, Minneapolis, Minnesota;* [3]*Veterans Affairs Healthcare System, Minneapolis, Minnesota;* [4]*Division of Gastroenterology, Beth Israel Deaconess Medical Center, Boston, Massachusetts;* [5]*Department of Medicine, University of Tennessee College of Medicine, Memphis, Tennessee;* [6]*Department of Medicine, Division of Gastroenterology, Vanderbilt University, Nashville, Tennessee; and* [7]*Department of Family Medicine, University of Michigan Medical School, Ann Arbor, Michigan*

This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e15. Learning Objective: Upon completion of this CME activity, successful learners will be able to identify pharmacologic treatment options for the management of individuals with IBS-C.

BACKGROUND & AIMS: Irritable bowel syndrome (IBS) is a common disorder of gut–brain interaction associated with significant disease burden. This American Gastroenterological Association guideline is intended to support practitioners in decisions about the use of medications for the pharmacological management of IBS-C and is an update of a prior technical review and guideline. **METHODS:** The Grading of Recommendations Assessment, Development and Evaluation framework was used to assess evidence and make recommendations. The technical review panel prioritized clinical questions and outcomes according to their importance for clinicians and patients and conducted an evidence review of the following agents: tenapanor, plecanatide, linaclotide, tegaserod, lubiprostone, polyethylene glycol laxatives, tricyclic antidepressants, selective serotonin reuptake inhibitors, and antispasmodics. The Guideline Panel reviewed the evidence and used the Evidence-to-Decision Framework to develop recommendations. **CONCLUSIONS:** The panel agreed on 9 recommendations for the management of patients with IBS-C. The panel made a strong recommendation for linaclotide (high certainty) and conditional recommendations for tenapanor, plecanatide, tegaserod, and lubiprostone (moderate certainty), polyethylene glycol laxatives, tricyclic antidepressants, and antispasmodics (low certainty). The panel made a conditional recommendation against the use of selective serotonin reuptake inhibitors (low certainty).

Keywords: Irritable Bowel Syndrome; Treatment; Symptoms; Quality of Life; Randomized Controlled Trial; Meta-Analysis; Linaclotide; Plecanatide; Lubiprostone; Tenapanor; Tegaserod; Polyethylene Glycol; Antispasmodic; Tricyclic Antidepressant; Selective Serotonin Reuptake Inhibitor.

This guideline is 1 of 2 related documents that provide updated evidence-based recommendations for the management of irritable bowel syndrome (IBS). Although this guideline focuses on the pharmacological management of IBS with predominant constipation, a separate and accompanying guideline focuses on pharmacological management of IBS with predominant diarrhea. Because these 2 documents serve as stand-alone guidelines that replace the prior technical review and guideline on the American Gastroenterological Association Guideline platform, sections of the documents and select recommendation statements are common to both guidelines.

Irritable bowel syndrome (IBS) is a common disorder of gut–brain interaction with a worldwide prevalence among adults between 4.1% (Rome IV criteria) and 10.1% (Rome III criteria).[1–3] IBS affects people regardless of race, age, or sex, but it is most common in women and younger individuals. Although not a life-threatening condition, IBS is associated with significant disease burden, including decrease in quality of life (QOL), elevated rates of psychological comorbidities, and high economic costs.[4–7] Patients with IBS report worse health-related QOL than patients with diabetes or end-stage renal disease.[8] The impact of IBS on daily functioning can be demonstrated by high rates of absenteeism (average of 13.4 days of work or school per year compared with 4.9 days for those without IBS) and presenteeism (87% report reduced productivity at work in the past week resulting in nearly 14 hours per week of lost

***Authors share co-first authorship.**

Abbreviations used in this paper: **AGA, American Gastroenterological Association; BSFS, Bristol Stool Form Scale; CIC, chronic idiopathic constipation; CSBM, complete spontaneous bowel movement; FDA, US Food and Drug Administration; GC-C, guanylate cyclase C; GRADE, Grading of Recommendations Assessments, Development and Evaluation; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with constipation; PEG, polyethylene glycol; PEG-E, polyethylene glycol with electrolytes; QOL, quality of life; RCT, randomized controlled trial; RR, relative risk; SAE, serious adverse event; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TIA, transient ischemic attack; TR, technical review.**

Most current article

© 2022 by the AGA Institute
0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2022.04.016

productivity due to IBS).[9–11] Socially, the impact of IBS on daily life can be seen in the negative impact of eating outside the home, going out with friends, traveling, and going to new or unfamiliar places.[12,13]

IBS with predominant constipation (IBS-C) is a subtype of IBS that accounts for more than one-third of IBS cases.[3] The IBS in America survey, conducted by the American Gastroenterological Association (AGA), found that individuals with IBS-C are more likely to report feeling self-conscious, avoiding sex, having difficulty concentrating, and not feeling able to reach one's full potential.[14] A positive diagnosis of IBS-C can be made on the basis of medical history and physical examination, evaluation of gastrointestinal symptoms (especially alarm signs), limited diagnostic testing, and use of the symptom-based Rome IV criteria.[15] The presence of alarm features, such as new symptom onset after age 50 years; rectal bleeding not attributable to hemorrhoids or anal fissures; unintentional weight loss; iron deficiency anemia; nocturnal diarrhea; and a family history of colon cancer, inflammatory bowel disease, or celiac disease, requires more patient-specific investigations.

Objective

Since the AGA published the first IBS technical review (TR) and guideline in 2014,[16,17] new pharmacological treatments have become available and new evidence has accumulated about established treatments. The purpose of these guidelines is to provide updated evidence-based recommendations for the pharmacological management of individuals with IBS-C based on a systematic and comprehensive synthesis of the literature. In addition, we included recommendations for the following 3 classes of pharmacotherapeutic agents for IBS: tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and antispasmodics, not specific to one bowel subtype, which were included in the prior TR and guideline.[16,17] Updated evidence-based recommendations for IBS with predominant diarrhea (IBS-D) are available in a separate guideline.

Target Audience

The target audience of these guidelines includes primary care and gastroenterology health care professionals, patients, and policy makers. These guidelines are not intended to impose a standard of care, rather they provide the basis for rational informed decisions for patients and health care professionals. Statements regarding the underlying values and preferences, as well as qualifying remarks accompanying each recommendation, should never be omitted when quoting or translating recommendations from these guidelines. Recommendations provide guidance for typical patients with IBS-C; no recommendation can consider all of the unique individual circumstances that must be accounted for when making recommendations for individual patients. However, discussions about benefits and harms can be used for shared decision making, especially for conditional recommendations when patient values and preferences are important to consider. These recommendations are summarized in Table 1 (Executive Summary of Recommendations).

Methods

Overview

This document represents the official recommendations of the AGA and was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. and adheres to best practices in guideline development, as outlined by the National Academy of Medicine (formerly Institute of Medicine) previously. Development of this guideline was fully funded by the AGA Institute.[18]

Guideline Panel Composition and Conflict of Interest

Members of the guideline and TR panels were selected on the basis of their clinical and methodological expertise after undergoing a vetting process that required disclosing all conflicts of interest. The TR panel consisted of 2 content experts with expertise in IBS (A.L., L.C.) and a guideline methodologist with expertise in evidence synthesis and GRADE (S.S.). This guideline was developed by a multidisciplinary panel that included a family medicine practitioner (J.H.), general gastroenterologist (W.S.), gastroenterologist with expertise in IBS (G.N.V), and a guideline methodologist (S.S.). Panel members disclosed all potential conflicts of interest. Conflicts were managed according to AGA policies, the National Academy of Medicine, and Guidelines International Network standards. The methodologist had no conflict of interest. No guideline panel member was excused from participation in the process owing to disqualifying conflict.

Scope

The guideline panel and TR team identified and formulated clinically relevant questions focused on pharmacological therapies for IBS-C. As this was an update of a prior IBS guideline published in 2014,[17] the authors identified new clinical questions and reviewed the evidence for pharmacological therapies from the prior guideline. This guideline provides new or updated recommendations for the following pharmacological therapies for IBS-C: tenapanor, plecanatide, linaclotide, tegaserod, and a review of the evidence and recommendations for lubiprostone and polyethylene glycol (PEG) laxatives. In addition, we included recommendations for 3 classes of pharmacotherapeutic agents for IBS (TCAs, SSRIs, and antispasmodics) that are not specific to one IBS bowel subtype and were included in the prior TR and guidelines.[16,17]

Formulation of Clinical Questions and Determining Outcomes of Interest

A protocol was developed *a priori* by the TR panel to guide the systematic review. The PICO format was used to outline the specific patient population (P), intervention (I), comparator (C), and outcome(s) for each clinical question. We focused on adults (aged 18 years and older) with IBS using symptom-based diagnostic criteria. The panel selected desirable (benefits) and undesirable (harms) patient-important outcomes that were consistent with the prior technical review. Only CRITICAL and IMPORTANT outcomes (for decision making) were summarized in the evidence profiles. The US Food and Drug Administration (FDA) responder end point for IBS-C was considered to be a CRITICAL outcome. However, when this end point was not

Table 1. Executive Summary of Recommendations

New or updated recommendations[a]	Strength of recommendation	Certainty of evidence
1. In patients with IBS-C, the AGA suggests using tenapanor	Conditional	Moderate
2. In patients with IBS-C, the AGA suggests using plecanatide	Conditional	Moderate
3. In patients with IBS-C, the AGA recommends using linaclotide	Strong	High
4. In patients with IBS-C, the AGA suggests using tegaserod Implementation remark: Tegaserod was reapproved for women under the age of 65 years without a history of cardiovascular ischemic events (such as myocardial infarction, stroke, TIA, or angina)	Conditional	Moderate
5. In patients with IBS-C, the AGA suggests using lubiprostone	Conditional	Moderate
6. In patients with IBS-C, the AGA suggests using PEG laxatives	Conditional	Low
7. In patients with IBS, the AGA suggests using TCAs	Conditional	Low
8. In patients with IBS, the AGA suggests against using SSRIs	Conditional	Low
9. In patients with IBS, the AGA suggests using antispasmodics	Conditional	Low

[a]For all recommendation statements, the comparator was no drug treatment.

available, adequate global relief was considered to be a CRITICAL outcome. For IBS-C, the FDA responder end point was defined as a participant who reports both a ≥30% reduction in average daily worst abdominal pain scores and an increase of ≥1 complete spontaneous bowel movements (CSBMs) per week compared with baseline for ≥6 of 12 weeks. The European Medicines Agency responder end point was similar to the FDA responder end point except it was for ≥13 of 26 weeks. The following outcomes were considered IMPORTANT outcomes: abdominal pain response, CSBM response, and improvement in IBS-QOL score. Undesirable outcomes included adverse effects leading to treatment discontinuation. For IBS-QOL score, the range is 0 to 100 and a minimal important difference is 14.[19] The minimal clinically meaningful improvement (often referred to as the smallest difference that patients care about) was defined by the authors as an improvement over placebo in an outcome of ≥10% (consistent with the prior TR[16]). This threshold was used to make contextualized judgments about imprecision.

Search Strategy

An experienced medical librarian conducted a comprehensive search of the following databases (Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, EMBASE, and Wiley Cochrane Library) from inception to April 21, 2020, using a combination of controlled vocabulary terms supplemented with keywords (see Supplementary Figure 1). To ensure that recent studies were not missed, searches were updated before external review. The search was limited to English language and human adults. The bibliography of prior guidelines and the included references were searched to identify relevant studies that may have been missed. In addition, content experts helped identify any ongoing studies.

Study Selection, Data Collection, and Analysis

The inclusion and exclusion criteria were based on the formulated clinical questions. Only randomized controlled trials (RCTs) conducted in adults with IBS evaluating interventions of interest were considered. The title and abstract of each identified reference were reviewed by 1 investigator (S.S.). Each full-text article was evaluated by all members of the TR team; any question or uncertainty was resolved by means of discussion with the team. If results were incomplete or unclear, study authors or study sponsors were contacted for additional information. Outcomes were abstracted and reported as failure of symptom relief (FDA responder), failure of abdominal pain response, failure of CSBM response, failure to achieve a clinically meaningful improvement in IBS-QOL, and adverse events leading to treatment discontinuation or other harm outcomes. Pooled relative risk (RR) or odds ratios and 95% CIs were calculated using the Mantel-Haenszel fixed-effects model (in the absence of heterogeneity and if fewer than 3 studies) or the DerSimonian-Liard random-effects model.[20] Statistical heterogeneity was assessed using the I^2 statistic. Direct comparisons were performed using RevMan, version 5.3 (Cochrane Collaboration, Copenhagen, Denmark). See Supplementary Figure 2 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

Certainty of the Evidence

Risk of bias was assessed using the Cochrane Risk-of-Bias Tool for RCTs and the certainty of evidence was assessed using the GRADE approach, which is the framework used for the development of AGA guidelines.[18] The certainty of evidence reflects the extent of our confidence in the estimates of effect. Evidence from RCTs start as high certainty and evidence derived from observational studies start as low certainty. For each outcome, the evidence is graded as high, moderate, low, or very low (Table 2). The evidence can be rated down for risk of bias, inconsistency, indirectness, imprecision, and publication bias. The certainty of evidence originating from observational studies can be rated up when there is a large magnitude of effect or dose–response relationship. Judgments about the certainty of evidence were determined via consensus and an

Table 2. Interpretation of Strong and Conditional Recommendations Using the Grading of Recommendations Assessments, Development, and Evaluation Framework

Implications	Strong recommendation	Conditional recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients consistent with his or her values and preferences. Use shared decision making. Decision aids may be useful in helping patients make decisions consistent with their individual risks, values and preferences.
For policy makers	The recommendation can be adapted as policy or performance measure in most situations	Policy making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision making is appropriate.

NOTE. Strong recommendations are indicated by statements that lead with "we recommend" and conditional recommendations are indicated by statements that lead with "we suggest."

overall judgment of certainty of evidence was made for each PICO. Evidence profiles were developed for each intervention using the GRADEpro Guideline Development Tool.[21] Therapies for which no new evidence was identified, the evidence is summarized from the prior TR and guideline.

Evidence to Recommendations

The guideline and TR panels met face to face to discuss the evidence and the guideline authors subsequently formulated the guideline recommendations. Based on the Evidence-to-Decision Framework, the panel considered the certainty of evidence, balance of benefit and harms, patient values and preferences, and (when applicable) feasibility, acceptability, equity, and resource use. For all recommendations, the panel reached consensus. The certainty of evidence and the strength of recommendation are provided for each clinical question. As per GRADE methodology, recommendations are labeled as "strong" or "conditional." The phrase "we recommend" indicates strong recommendations and "we suggest" indicates conditional recommendations. Table 3 provides the suggested interpretation of strong and weak recommendations for patients, clinicians, and health care policy makers. For all the recommendations, the intervention is compared with "not using the intervention" or the treatment is recommended or suggested "over no drug treatment." The comparator is not explicitly included in the recommendation statement to avoid redundancy.

Review Process

This guideline was submitted for public comment and internal review and was approved by the AGA Governing Board.

Recommendations

A summary of all the recommendations is provided in Table 1. A description of included studies is provided in Table 4 and an overview of the relative and absolute effect estimates for the critical outcomes is provided in Table 5. For all recommendations in this document, the pharmacological agent was compared with "no drug treatment."

Table 3. Interpretation of the Certainty in Evidence of Effects using the Grading of Recommendations Assessments, Development and Evaluation Framework

Certainty of evidence	Definition
High ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate ⊕⊕⊕◯	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low ⊕⊕◯◯	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low ◯◯◯◯	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

Table 4. Study Characteristics and Relevant Patient-Important Outcomes

Study and setting	Patients	Intervention	Symptom relief (FDA responder)	Global symptoms	Abdominal pain	CSBM	IBS-QOL
Tenapanor for IBS-C							
Chey[25] 2020 T3MPO-1 92 US sites n = 629	Outpatients (18–75 y) with IBS-C (Rome III)[a]	Tenapanor 50 mg bid	Reduction of ≥30% from baseline in worst abdominal pain and stool frequency responder ≥1 CSBM/wk from baseline) in the same week for ≥6 of 12 wk	Weekly adequate relief and degree of relief of IBS symptoms (using a yes or no question	Reduction of ≥30% from baseline in worst abdominal pain for ≥6 of 12 wk	≥1 CSBM/wk from baseline) for ≥6 of 12 wk	Not reported
Chey[26] 2021 T3MPO-2 92 US sites n = 620	Outpatients (18–75 y) with IBS-C (Rome III)[a]	Tenapanor 50 mg bid	Reduction of ≥30% from baseline in worst abdominal pain and stool frequency responder ≥1 CSBM/wk from baseline) in the same week for ≥13 of 26 wk	Weekly adequate relief and degree of relief of IBS symptoms (using a yes or no question	Reduction of ≥30% from baseline in worst abdominal pain for ≥13 of 26 wk	≥1 CSBM/wk from baseline) for ≥13 of 26 wk	Change from baseline in the IBS-QOL questionnaire score
Chey[24] 2017 Phase 2b 79 sites n = 356	Outpatients (18–75 y) with IBS-C (Rome III)[a]	Tenapanor 50 mg bid (other arms were 5 and 20 mg bid)	Reduction of ≥30% from baseline in worst abdominal pain and ≥1 CSBM/wk from baseline) in the same week for ≥6 of 12 wk	Not measured	Reduction of ≥30% from baseline in worst abdominal pain for ≥6 of 12 wk	≥1 CSBM/wk from baseline) for ≥6 of 12 wk	Not reported

Table 4. Continued

Study and setting	Patients	Intervention	Symptom relief (FDA responder)	Global symptoms	Abdominal pain	CSBM	IBS-QOL
Plecanatide for IBS-C Brenner[32] 2018 Study 1 130 US sites n = 1054 Study 2 140 US sites n = 1135	Outpatients 18–85 y with IBS-C (Rome III) with, at baseline, ≥25% of SBMs (BSFS score of 1 or 2) and <25% of reported SBMs (BSFS score of 6 or 7)	Plecanatide 3 mg or 6 mg once daily	Reduction of ≥30% from baseline in worst abdominal pain and stool frequency responder (reported an increase of ≥1 CSBM/wk from baseline) in the same week for ≥6 of 12 wk	—	Reduction of ≥30% from baseline in weekly average worst abdominal pain score for ≥6 of 12 wk	≥1 CSBM from baseline in at least 6 of 12 wk	—
Linaclotide for IBS-C Yang[41] 2018 98 centers (China, United States, Canada, Australia, and New Zealand)	Outpatients, aged ≥18 y, with IBS-C (Rome III) with, at baseline, <3 BMs/wk and ≥1 additional bowel symptom during >25% of BMs (straining, lumpy/hard stools, or sensation of incomplete evacuation)	Linaclotide 290 μg once daily	Both a reduction of ≥30% in average weekly abdominal pain or abdominal discomfort score and an increase in ≥1 CSBMs/wk from baseline for ≥6 of 12 wk	Relief of IBS symptoms weekly scores (IBS symptom severity, constipation severity, and adequate relief for ≥6 of 12 wk	Reduction of ≥30% from baseline in the weekly abdominal pain score for ≥9 of 12 wk	≥3 CSBMs/wk from baseline and an increase in ≥1 CSBM/wk for ≥9 of 12 wk	Not reported
Chey[40] 2012 102 centers (United States)	Outpatients, aged ≥18 y, with IBS-C (Rome II) with, at baseline, <3 BMs/wk and ≥1 symptom during >25% of BMs (straining, lumpy/hard stools, or sensation of incomplete evacuation)	Linaclotide 290 μg once daily	Reduction of ≥30% in average daily worst abdominal pain score and an increase in ≥1 CSBM/wk from baseline in the same week for ≥6 of 12 wk	Adequate relief of IBS symptoms for ≥6 of 12 wk	Reduction of ≥30% from baseline in the average daily abdominal pain score for ≥9 of 12 wk	≥3 CSBMs/wk from baseline and an increase in ≥1 CSBMs/wk for ≥9 of 12 wk	No responder definition, mean change from baseline to wk 12 reported in a separate publication

Table 4. Continued

Study and setting	Patients	Intervention	Symptom relief (FDA responder)	Global symptoms	Abdominal pain	CSBM	IBS-QOL
Rao[38] 2012 118 centers (111 in the United States, 7 in Canada)	Outpatients, aged ≥18 y, with IBS-C (Rome II) with, at baseline, <3 BMs/wk and ≥1 symptom during >25% of BMs (straining, lumpy/hard stools, or sensation of incomplete evacuation)	Linaclotide 290 μg once daily	Reduction of ≥30% in average daily worst abdominal pain score AND an increase in ≥1 CSBM/wk from baseline for ≥6 of 12 wk	Adequate relief of IBS symptoms (12-wk change from baseline) or change from baseline for ≥6 of 12 wk	Reduction of ≥30% from baseline in the average daily abdominal pain score for ≥9 of 12 wk	≥3 CSBMs/wk from baseline and an increase in ≥1 CSBM/wk for ≥9 of 12 wk	No responder definition, mean change from baseline to wk 12 reported in a separate publication
Johnston[39] 2010 92 centers (US and Canada)	Outpatients, aged ≥18 y, with IBS-C (Rome II) with, at baseline, <3 BMs/wk and ≥1 symptom during >25% of BMs (straining, lumpy/hard stools, or sensation of incomplete evacuation)	Linaclotide 290 μg once daily	Not reported	Adequate relief of IBS symptoms for ≥9 of 12 wk	Rot reported	≥3 CSBMs/wk from baseline and an increase in ≥1 CSBM/wk for ≥9 of 12 wk	Responder definition: change from baseline in the overall IBS-QOL score of ≥14
Tegaserod for IBS-C							
Muller-Lissner[49] (Study 301) 2001 92 centers (Europe, South Africa, United States)	Outpatients, aged ≥18 y, with IBS-C (Rome I) and have ≥2 of 3 constipation symptoms ≥25% of the time during the 3 mo before the study (<3 BMs/wk, hard/lumpy stools, straining)	Tegaserod, 2 mg bid or 6 mg bid	Both a reduction of ≥30% in average weekly abdominal pain and an increase in ≥1 BM/wk from baseline for ≥6 of 12 wk	IBS symptoms "completely or considerably" relieved for ≥6 of 12 wk or at least "somewhat" relieved for all 12 wk	Mean reduction in abdominal pain/ discomfort of ≥40% and a reduction of ≥20 mm (VAS, 0–100) over 12 wk	An increase of ≥1 BMs/wk for ≥6 of 12 wk	Change from baseline to wk 12 in IBS-QOL Global Score

Table 4. Continued

Study and setting	Patients	Intervention	Symptom relief (FDA responder)	Global symptoms	Abdominal pain	CSBM	IBS-QOL
Novick[51] (Study 358) 2002 131 centers (North America, Europe)	Outpatients, women, aged ≥18 y, with IBS-C (Rome I) and have ≥2 of 3 constipation symptoms ≥25% of the time during the 3 mo before the study (<3 BMs/wk, hard/lumpy stools, straining) At least mild pain (>1.5 on a 7-point scale) and at least normal stool consistency (>3.5 on a 7-point scale) during the baseline period	Tegaserod, 2 mg bid or 6 mg bid	Both a reduction of ≥30% in average weekly abdominal pain and an increase in ≥1 BMs/wk from baseline for ≥6 of 12 wk	IBS symptoms "completely" or "considerably" relieved for ≥6 of 12 wk or at least "somewhat" relieved for all 12 wk	Not reported	An increase of ≥1 BMs/wk for ≥6 of 12 wk	—
Lefkowitz[50] (Study 351) 1999 49 centers (North and South America, South Africa)	Outpatients, aged ≥18 y, with IBS-C (Rome I)	Tegaserod, 2 mg bid or 6 mg bid	Both a reduction of ≥30% in average weekly abdominal pain and an increase in ≥1 BMs/wk from baseline for ≥6 of 12 wk	IBS symptoms "completely" or "considerably" relieved for ≥6 of 12 wk or at least "somewhat" relieved for all 12 wk	Mean reduction in abdominal pain/ discomfort of ≥40% and a reduction of ≥20 mm (VAS, 0–100) over 12 wk	An increase of ≥1 BMs/wk for ≥6 of 12 wk	Change from baseline to wk 12 in IBS-QOL Global Score
FDA[52] (Study 307) 2018 92 centers (US and Canada)	Outpatients, aged ≥18 y, with IBS-C (Rome I)	Tegaserod, 2 mg bid or 6 mg bid	Both a reduction of ≥30% in average weekly abdominal pain and an increase in ≥1 BMs/wk from baseline for ≥6 of 12 wk	IBS symptoms "completely" or "considerably" relieved for ≥6 of 12 wk or at least "somewhat" relieved for all 12 wk	Mean reduction in abdominal pain/ discomfort of ≥40% and a reduction of ≥20 mm (VAS, 0–100) over 12 wk	An increase of ≥1 BMs/wk for ≥6 of 12 wk	Responder definition: change from baseline in the overall IBS-QOL score of ≥14

bid, twice daily.

[a]All patients met Rome III criteria for IBS-C and were required to meet the following clinical criteria during the 2-week baseline run-in period: (i) a mean abdominal pain score of at least 3 on a 0- to 10-point numeric rating scale where a score of 0 indicates no pain and 10 indicates very severe pain; (ii) less than 3 complete spontaneous bowel movements (CSBMs) per week, where a CSBM is defined as a spontaneous bowel movement (SBM) that is associated with a sense of complete evacuation (an SBM is a bowel movement occurring in the absence of laxative use); and (iii) less than or equal to 5 SBMs per week.

Table 5. An Overview of the Effect Estimates for the Newer Pharmacological Agents

Critical outcomes	No. of participants (studies)	RR (95% CI)	Absolute effects (95% CI)	Certainty of evidence
Tenapanor				
Failure of symptom relief (FDA responder definition)	1372 (2 RCTs)	0.84 (0.79–0.90)	125 fewer per 1000 (from 78 fewer to 165 fewer)	⨁⨁⨁◯ MODERATE
AE (diarrhea) leading to treatment discontinuation	1382 (3 RCTs)	6.27 (2.99–13.15)	61 more per 1000 (from 23 more to 141 more)	⨁⨁⨁◯ MODERATE
Plecanatide				
Failure of symptom relief (FDA responder definition)	1632 (3 RCTs)	0.87 (0.83–0.92)	108 fewer per 1000 (from 67 fewer to 141 fewer)	⨁⨁⨁◯ MODERATE
AE leading to treatment discontinuation	1632 (3 RCTs)	5.68 (2.10–15.39)	23 more per 1000 (from 5 more to 70 more)	⨁⨁⨁◯ MODERATE
Linaclotide				
Failure of symptom relief (FDA responder definition)	2443 (3 RCTs)	0.81 (0.77–0.85)	154 fewer per 1000 (from 122 fewer to 187 fewer)	⨁⨁⨁⨁ HIGH
AE leading to treatment discontinuation	2612 (3 RCTs)	14.94 (4.65–8.03)	32 more per 1000 (from 8 more to 108 more)	⨁⨁⨁◯ MODERATE
Tegaserod				
Failure of symptom relief (FDA responder definition)	2883 (4 RCTs)	0.87 (0.8–0.93)	100 fewer per 1000 (from 54 fewer to 145 fewer)	⨁⨁⨁◯ MODERATE
AE leading to treatment discontinuation	2939 (4 RCTs)	1.30 (0.97–1.74)	15 more per 1000 (from 2 fewer to 37 more)	⨁⨁⨁◯ MODERATE
AE leading to treatment discontinuation (age <65 years and low CV risk)	2752 (4 RCTs)	1.37 (0.99–1.88)	17 more per 1000 (from 0 fewer to 40 more)	⨁⨁⨁◯ MODERATE

AE, adverse event; CV, cardiovascular.

1. Should Tenapanor Be Used in Patients With Irritable Bowel Syndrome With Constipation?

The AGA suggests using tenapanor in patients with IBS-C.
(Conditional recommendation, moderate certainty)

Tenapanor is a first-in-class, small-molecule inhibitor of the gastrointestinal sodium/hydrogen exchanger isoform 3, which is expressed on the apical surface of the small intestine and colon and is primarily responsible for the absorption of sodium.[22] It is locally acting and minimally absorbed. Tenapanor decreases absorption of sodium and phosphate and increases water secretion into the intestinal lumen and has been found to have antinociceptive effects.[23] Tenapanor is FDA-approved for the treatment of IBS-C at a dosage of 50 mg twice daily.

Summary of the evidence. Three placebo-controlled RCTs (1 phase 2b and 2 phase 3) have evaluated the efficacy and safety of tenapanor in patients with IBS-C.[24–26] The phase 2b RCT was a dose-ranging study (5, 20, and 50 mg twice daily) in which 89 of the 356 patients with IBS-C were randomized to receive the 50-mg dosage of tenapanor and 90 patients to placebo for 12 weeks.[24] The 2 phase 3, placebo-controlled RCTs (T3MPO-1 and T3MPO-2) randomized patients with IBS-C to receive tenapanor 50 mg twice daily or placebo. One of the phase 3 RCTs (T3MPO-1) included 307 patients with IBS-C who received tenapanor and 299 who received placebo for 12 weeks, followed by a 4-week randomized withdrawal period.[25] A second phase 3 RCT (T3MPO-2) included 293 patients with IBS-C randomized to receive tenapanor and 300 patients to receive placebo for 26 weeks.[26] Patients included in these trials met Rome III criteria for IBS-C[27] and reported (during the 2-week baseline period) an average weekly stool frequency of ≤5 SBMs and ≤3 CSBMs, an average weekly stool consistency of Bristol Stool Form Scale (BSFS)[28] type ≤3, an average weekly abdominal pain score of ≥3 on a scale of 0–10 (0 indicating no pain and 10 the worst imaginable pain), and no liquid stools for any SBMs or mushy stools for >1 SBM. In the 2 phase 3 trials, the primary efficacy responder definition was the FDA responder end point for IBS-C.[29] In the phase 2b trial, the primary efficacy end point was the CSBM responder rate, which was defined as the proportion of patients with an increase of ≥1 CSBM per week compared with baseline for at least 6 of the 12 treatment weeks. The FDA responder was a secondary end point.[24]

Benefits. In total, 688 patients with IBS-C were treated with tenapanor 50 mg twice daily and 684 were treated with placebo for a duration of 12 weeks. Compared with placebo, patients who received tenapanor experienced greater symptom relief using the FDA responder end point for IBS-C across the 3 studies (RR, 0.84; 95% CI, 0.79–0.90).

The FDA end point for IBS-C was met by 34.1% in the tenapanor group vs 21.7% in the placebo group.[24–26] In 1 of the phase 3 trials that was 26 weeks in duration, a considerably greater proportion of patients in the tenapanor group met the European Medicines Agency responder end point compared with placebo (35.5% vs 24.3%).[26] With respect to individual symptoms, tenapanor demonstrated a higher success rate compared with placebo for improvement in abdominal pain (RR, 0.81; 95% CI, 0.73–0.88) with a risk difference of 12.1% and improvement in CSBM response (RR, 0.83; 95% CI, 0.77–0.90) with a risk difference of 11.3% over 12 weeks.[24–26] In the 2 phase 3 trials, a greater proportion of patients with IBS-C taking tenapanor (58.1%) reported adequate relief of IBS symptoms at 12 weeks of treatment compared with placebo (41.1%) (RR, 0.71; 95% CI, 0.61–0.82).[25,26]

Adverse events. Diarrhea was the most common adverse event, occurring in 14.8% of patients receiving tenapanor compared with 2.3% of patients receiving placebo. Diarrhea led to discontinuation of medication in 6.6% of patients receiving tenapanor and 1.0% receiving placebo. With respect to serious adverse events (SAEs) across the 3 trials, 11 patients receiving tenapanor experienced an SAE (eg, diarrhea, abdominal pain, nausea, chronic obstructive pulmonary disease, panic, osteoarthritis, migraine, and depression) compared with 7 patients in the placebo group. Only the diarrhea SAE was judged by the investigator to be "possibly related" to treatment. No deaths occurred in the trials.

Certainty in evidence of effects. The panel rated down for imprecision (FDA and CSBM responder end points) because the CI crossed our threshold of a clinically meaningful difference. The trials were considered to have a low risk of bias. The overall certainty in evidence for tenapanor was MODERATE. See Supplementary Table 1 for the full evidence profile.

Rationale. The panel made a conditional recommendation for the use of tenapanor in individuals with IBS-C, noting the low rates of diarrhea leading to treatment discontinuation and improvement in abdominal pain and CSBM response (including the FDA combined end point) compared with placebo. Although not included in the evidence profiles, tenapanor was associated with improvement in other clinically important end points, including SBM frequency; stool consistency; and global measures of IBS severity, constipation severity, and treatment satisfaction compared with placebo.[24–26] Diarrhea was the most common adverse event, leading to discontinuation of medication in 6.6% of patients in the tenapanor group compared with 1.0% in the placebo group. Importantly, the efficacy of tenapanor is maintained beyond the initial 12 weeks, as shown by results of the T3MPO-2 trial in which the treatment period was 26 weeks. The T3MPO-1 trial included a 4-week randomized withdrawal period after completion of the 12-week treatment period and patients who were switched from placebo to tenapanor during this 4-week period had a significant improvement in weekly CSBM frequency compared with those who were switched from tenapanor to placebo.

2. Should Plecanatide Be Used in Patients With Irritable Bowel Syndrome With Constipation?

The AGA suggests using plecanatide in patients with IBS-C.
(Conditional recommendation, moderate certainty)

Plecanatide is a nonabsorbed 16-amino acid peptide structurally similar to uroguanylin, which, like linaclotide, stimulates the guanylate cyclase C (GC-C) receptor on enterocytes via the secondary messenger cyclic guanosine monophosphate, which activate the cystic fibrosis transmembrane conductance regulator, causing fluid and electrolyte secretion[30] and reducing visceral hypersensitivity in an animal model.[31] In contrast to linaclotide, which is not pH-sensitive, plecanatide has a higher affinity to the GC-C receptor in the more acidic environment seen in proximal duodenum. Plecanatide is FDA-approved for the treatment of IBS-C and chronic idiopathic constipation (CIC) at a dosage of 3 mg once daily.

Summary of the evidence. In 2 large phase 3 trials,[32] the efficacy of 2 dosages of plecanatide (3 mg and 6 mg once daily) was assessed over 12 weeks in patients with IBS-C. Patients included in these trials met Rome III criteria for IBS-C[27] and reported (during the 2-week baseline period) no more than 3 CSBMs or >6 SBMs per week, and an average worst abdominal pain score of ≥3 on a scale from 0 to 10. Patients could not report a worst abdominal pain score of 0 for more than 2 days or BSFS score of 7 for 1 or more days, or a BSFS[28] score of 6 for more than 1 day. The primary efficacy outcomes were the FDA responder end point for IBS-C,[29] along with the abdominal pain and CSBM responder definitions (see Table 4). A phase 2b dose-ranging trial that included a 3-mg treatment arm, published only in abstract form, was also included.[33]

Benefits. In total, 814 patients with IBS-C were treated with plecanatide (3 mg) and 818 with placebo. Compared with placebo, patients who received plecanatide showed greater symptom relief using the FDA responder end point for IBS-C (RR, 0.87; 95% CI, 0.83–0.92). The FDA end point for IBS-C was met by 27.4% in the plecanatide group vs 16.9% in the placebo group. With respect to individual symptoms, plecanatide demonstrated a higher success rate over the initial 12 weeks, compared with placebo, for improvement in abdominal pain (RR, 0.86; 95% CI, 0.81–0.92) with a risk difference of 10.1% and CSBM (RR, 0.84; 95% CI, 0.79–0.91) with a risk difference of 10.9%.

Adverse events. Diarrhea was the most common adverse event. In the phase 3 trials, diarrhea was reported by 4.3% of patients receiving plecanatide compared with 1% of patients receiving placebo. Diarrhea led to discontinuation in 1.2% of patients receiving plecanatide (3 mg) compared with 0% receiving placebo. The incidence of SAEs was 0.8%, which was similar in patients treated with plecanatide and placebo. There were no diarrhea-related SAEs, but 1 death was reported (drowning) that was deemed unrelated to the study drug.

Certainty in evidence of effects. The panel rated down for imprecision across many of the outcomes because the CI crossed our threshold of a clinically meaningful difference. The trials were considered to have low risk of bias. The overall certainty in evidence for plecanatide was MODERATE. See Supplementary Table 2 for the full evidence profile.

Rationale. In individuals with IBS-C, plecanatide treatment results in greater improvement in the FDA end point for IBS-C, as well as the components of the FDA end point (ie, abdominal pain and CSBM response). However, the improvement in these end points may be small in some patients. The panel made a conditional recommendation for the use of plecanatide in individuals with IBS-C. Although not included in the evidence profiles, plecanatide was associated with improvement in stool frequency, bloating, straining, and global measures of treatment satisfaction compared with placebo.[32] Diarrhea was the most common adverse event (4.3% plecanatide vs 1.0% placebo); 1.2% of patients withdrew from the trials due to diarrhea from plecanatide. The odds of diarrhea and diarrhea-related withdrawals were similar between the 2 GC-C agonists, plecanatide and linaclotide, based on a meta-regression analysis, which controlled for differences in diarrhea rates in the placebo arm.[34]

3. Should Linaclotide Be Used in Patients With Irritable Bowel Syndrome With Constipation?

The AGA recommends using linaclotide in patients with IBS-C.
(Strong recommendation, high certainty in the evidence of effects)

Linaclotide is a nonabsorbed 14-amino acid peptide that, like plecanatide, stimulates the GC-C receptor on enterocytes that results in intestinal chloride and bicarbonate secretion and, in animal models, inhibits colonic nociceptors.[35–37] Linaclotide is FDA-approved for the treatment IBS-C at a dosage of 290 μg once daily and for CIC at dosages of 72 μg and 145 μg once daily.

Summary of the evidence. The 2014 TR reported on data from 3 RCTs (2 phase 3 RCTs and 1 phase 2b RCT)[38–40] that included 1773 patients with IBS-C (linaclotide n = 890; placebo, n = 883). Since 2014, a third 12-week phase 3 trial[41] has been published that included 839 patients (mean age 41 years; 82% were female) from China (79%), Oceania (5%), and North America (16%). This trial included patients who met the Rome III IBS criteria.[42] To be included in this study, patients were required to report (during the 2-week baseline period) an average of $\leq$5 SBMs per week and <3 CSBMs per week and had to report abdominal pain $\geq$2 days each week with an average score $\geq$3.0 on a 0- to 10-point numerical rating scale (0 indicating no pain and 10 the worst imaginable pain). Patients were excluded if they reported BSFS score of 6 for >1 SBM or 7 for any SBM. There were 2 co-primary responder end points that consisted of improvement in weekly abdominal pain or abdominal discomfort score and in weekly IBS degree of relief score for $\geq$6 of 12 weeks (Table 4).

Benefits. In the third phase 3 trial,[41] 60.0% of patients receiving linaclotide reported $\geq$30% reduction in abdominal pain/discomfort compared with 48.8% of patients receiving placebo and 31.7% of patients receiving linaclotide reported an IBS relief score of $\leq$2 (ie, "considerably relieved" or "completely relieved") compared with 15.4% of patients receiving placebo. In addition, the FDA end point for IBS-C was met by 34.8% in the linaclotide group vs 21.3% in the placebo group, which was similar to previous trials.[38,43]

The overall efficacy of linaclotide was reanalyzed including data from this new study. Across the 4 RCTs, a total of 1307 patients were treated with linaclotide (290 μg) and 1305 with placebo. Compared with placebo, patients who received linaclotide had greater symptom relief using the FDA responder end point for IBS-C (RR, 0.81; 95% CI, 0.77–0.85). The FDA end point for IBS-C was met by 34.0% in the linaclotide group vs 18.8% in the placebo group. Similarly, compared with placebo, patients who received linaclotide showed greater improvement in the global assessment measure of adequate relief of IBS-C symptoms over the first 12 weeks (RR, 0.71; 95% CI, 0.67–0.76). With respect to individual symptoms, a greater proportion of patients who were treated with linaclotide reported improvement in abdominal pain (RR, 0.83; 95% CI, 0.78–0.88) and CSBMs (RR, 0.86; 95% CI, 0.83–0.89) compared with placebo over the initial 12 weeks.

Adverse events. Diarrhea was the most common adverse event, occurring in 16.3% of patients receiving linaclotide compared with 2.3% of patients receiving placebo. Linaclotide was associated with more discontinuations (3.4%) compared with placebo (0.2%) (RR, 14.94; 95% CI, 4.65–48.03) due to diarrhea. No SAEs due to diarrhea and no deaths were reported in any of the trials.

Certainty in evidence of effects. The individual trials were considered to have a low risk of bias. The panel rated down for inconsistency (IBS-QOL) and imprecision (adverse events leading to treatment discontinuation). The overall certainty in evidence for linaclotide was HIGH. See Supplementary Table 3 for the full evidence profile.

Rationale. After reviewing the additional evidence, the panel made a strong recommendation for the use of linaclotide in individuals with IBS-C. Across 4 RCTs, linaclotide improved global assessment of IBS-C symptoms (FDA responder), abdominal pain, CSBM response, as well as adequate global response (although not shown in the evidence profile). The addition of a third phase 3 trial,[41] which was performed predominantly in China, supports the efficacy of linaclotide for the treatment of IBS-C. The beneficial effects on linaclotide across all outcomes was very similar to that found in our prior TR, which did not include this third phase 3 trial. A recent network meta-analysis ranked linaclotide first in efficacy among secretagogues for IBS-C,[44] although head-to-head trials are lacking. The rate of

diarrhea is higher with linaclotide than placebo (16.2% vs 2.3%) and resulted in more discontinuations (3.4% vs 0.23%); however, no SAEs due to diarrhea were reported in any of the trials. It is worth noting that in the third phase 3 trial,[41] fewer patients reported diarrhea (9.4%) and the withdrawal rate because of diarrhea was lower (0.7%) than in previous RCTs with linaclotide. Although diarrhea was reported more commonly with linaclotide than with other secretagogues, particularly plecanatide, which is also a GC-C receptor agonist, a meta-regression analysis that controlled for differences in diarrhea rates in the placebo arm found the rates of diarrhea and diarrhea-related withdrawals were similar between the 2 GC-C agonists.[34]

4. Should Tegaserod Be Used in Patients With Irritable Bowel Syndrome With Constipation?

The AGA suggests using tegaserod in patients with IBS-C.
(Conditional recommendation, moderate certainty)
Implementation remark: Tegaserod was reapproved for women under the age of 65 years without a history of cardiovascular ischemic events (such as myocardial infarction, stroke, transient ischemic attack, or angina)

Tegaserod is a partial agonist of the 5-HT_4 receptor, which stimulates gastrointestinal motility and increases fluid in the gastrointestinal tract. Tegaserod was approved by the FDA in 2002 for short-term treatment of IBS-C in women and in 2004 for CIC in men and women under the age of 65 years. In 2007, the FDA requested withdrawal from the market due to a retrospective analysis of clinical trials that showed a small but higher rate of cardiovascular ischemic events with tegaserod (13 of 11,614 [0.11%]) compared with placebo (1 of 7031 [0.01%]).[45] However, subsequent observational studies failed to find an association between tegaserod and adverse cardiovascular outcomes.[46,47] Recently, the FDA re-examined the data and recommended a limited reapproval of tegaserod 6 mg twice a day for women with IBS-C, under 65 years of age, without a history of myocardial infarction, stroke, transient ischemic attack (TIA), or angina. The current analysis reviews the efficacy of tegaserod in women with IBS-C and in the subgroup of women without cardiovascular events and <1 cardiovascular risk factor; these were the patient populations for which the FDA responder end point was available. The incidence of adverse events was only assessed in women under the age of 65 years without a history of cardiovascular ischemic events, as tegaserod is currently FDA-approved for this patient population only. A pooled analysis of the 4 RCTs analyzing the safety and efficacy of tegaserod in women with low cardiovascular risk was published recently.[48]

Summary of the evidence. Our current analyses are limited to women with IBS-C receiving 6 mg twice daily of tegaserod (n = 1450) or placebo (n = 1433). Four 12-week phase 3 RCTs (Study 301,[49] Study 351,[50] Study 358,[51] and Study 307[52]) were conducted before the initial FDA approval in 2002. Three trials (Study 301, Study 307, and Study 351) included both men and women and 2 doses of tegaserod (2 mg and 6 mg) and the fourth trial (Study 358) included women only and a single dosage (6 mg twice daily) of tegaserod. One trial (Study 307) included a dosage escalation from 2 mg to 6 mg twice daily according to response (65% of patients increased the dosage after the first month of treatment). Patients included in these trials met Rome I criteria for IBS-C, were required to have 2 of 3 constipation criteria (ie, fewer than 3 BMs per day, hard or lumpy stools, or straining at least 25% of the time) and reported at least mild abdominal pain during the 4-week baseline period. The FDA end point for these trials differed slightly from the recommended FDA responder end point because these trials were conducted before the 2012 FDA Guidance for IBS treatment trials.[29] In these trials, the modified FDA responder end point was defined as $\geq$30% improvement in abdominal pain or discomfort, with an increase of $\geq$1 BM per week from baseline for $\geq$6 of 12 weeks. The Subject's Global Assessment of Overall IBS Relief was assessed by asking patients to rate their relief of overall IBS symptoms compared with the way they felt before entering the study. Possible answers were completely relieved, considerably relieved, somewhat relieved, unchanged, or worse. Responders were defined as patients who were "completely relieved"'or "considerably relieved" for at least 50% of the weeks at the end point or "somewhat relieved" 100% of the weeks at the end point. Abdominal pain and discomfort responder was defined as a $\geq$2-point improvement on a 6 or 7-point numeric rating scale for $\geq$6 of 12 weeks. Furthermore, these trials assessed frequency of BMs and not SBMs or CSBMs.

Benefits. Compared with placebo, women with IBS-C who received tegaserod 6 mg twice daily showed greater symptom relief using the FDA responder end point for IBS-C (RR, 0.87; 95% CI, 0.81 to 0.93). The FDA end point for IBS-C was met by 35.1% in the tegaserod group vs 23.4% in the placebo group. For the Subject's Global Assessment for Overall IBS Relief, tegaserod demonstrated greater response over the 12 weeks compared with placebo (RR, 0.85; 95% CI, 0.74 to 0.97). Tegaserod was associated with a 52.7% in global relief (Subject's Global Assessment Overall IBS Relief) compared with 44.8% responder rate for placebo. With respect to individual symptoms, tegaserod was also associated with improvement in abdominal pain or discomfort in 22.4% of patients in the tegaserod group vs 17.6% in the placebo group (RR, 0.92; 95% CI, 0.87 to 0.97). Use of tegaserod was associated with improvement in BM frequency in 65.6% of patients receiving tegaserod vs 51.2% of patients receiving placebo (RR, 0.71; 95% CI, 0.65 to 0.77) over the 12 weeks of treatment. Finally, compared with placebo, the mean difference in overall IBS-QOL score from baseline to week 12 was an increase in 1.21 points with tegaserod (95% CI, −0.76 to 3.18). Analyses limited to women with IBS-C without cardiovascular risks showed similar results (see Supplementary Table 4).

Adverse events. Overall, the most common reasons for discontinuation in patients taking tegaserod were diarrhea (1.6%) and headaches (1.0%).[53] Because of a possible signal of cardiovascular risk with tegaserod, a retrospective analysis of clinical trials was performed in 2007 and showed a higher rate of ischemic cardiovascular events with tegaserod (13 of 11,614 [0.11%]) compared with placebo (1 of 7031 [0.01%]).[45] The cardiovascular events in the tegaserod group were myocardial infarction (n = 3 [0.03%]), stroke (n = 3 [0.03%]), cardiovascular death (n = 1 [0.03%]), unstable angina (n = 6 [0.05%]), and TIA (n = 1 [0.01%]). However, large epidemiological studies failed to find differences in cardiovascular events in patients taking tegaserod vs matched individuals not taking tegaserod.[47] Subsequent review of the clinical trial data found that the risk for cardiovascular events occurred predominantly in individuals with history of cardiovascular ischemic events (such as myocardial infarction, stroke, TIA, or angina) or known cardiovascular risk factors (such as hypertension, tobacco use, diabetes, hypercholesterolemia, age ≥55 years, and obesity).[52] Subsequently, 2 independent groups adjudicated the adverse events and found fewer cardiovascular events attributable to tegaserod in women under the age of 65 years without cardiovascular disease.[52] In this subgroup of women, the rates of discontinuation were 6.2% (tegaserod) and 4.5% (placebo) (RR, 1.37; 95% CI, 0.99–1.88).

Certainty in evidence of effects. With the exception of BM frequency, we rated down for imprecision because the CIs for the other outcomes crossed our threshold for clinically meaningful differences. The overall certainty in evidence for tegaserod was MODERATE. See Supplementary Table 4 for the full evidence profile.

Rationale. The panel made a conditional recommendation for the use of tegaserod in individuals with IBS-C, noting that the FDA reapproval is for women under the age of 65 years without a history of cardiovascular ischemic events (such as myocardial infarction, stroke, TIA, or angina). In patients with IBS-C, treatment with tegaserod probably results in greater improvement in the modified FDA end point for IBS-C, global relief, abdominal pain/discomfort, and BM frequency compared with placebo; however, there was no improvement in overall QOL. Tegaserod was generally well tolerated, with a small increase in the number of patients who withdrew due to adverse effects compared with placebo. Cardiovascular risks appear to be limited in women under the age of 65 years who do not have a history of cardiovascular ischemic events. Although not included in our evidence synthesis, additional randomized, double-blind, placebo-controlled trials studies conducted in Asia-Pacific[54] and Nordic countries[55] after the initial FDA approval also showed a benefit of tegaserod in IBS-C. Also, patients who have recurrence of IBS-C symptoms after initial response to 4 weeks of treatment with tegaserod may benefit from a second course.[56]

Review of evidence from the prior technical review and guideline from 2014. Evidence for the following interventions was also reviewed: lubiprostone, PEG laxatives, alosetron, loperamide, TCAs, SSRIs, and antispasmodics.[16]

5. Should Lubiprostone Be Used in Patients With Irritable Bowel Syndrome With Constipation?

The AGA suggests using lubiprostone in patients with IBS-C.
(Conditional recommendation, moderate certainty)

This recommendation is unchanged from the 2014 IBS guideline.[17] Lubiprostone is a chloride channel type 2 activator that increases chloride influx into the lumen of the gastrointestinal tract, resulting in acceleration of intestinal transit.[57] Lubiprostone is also approved for the treatment of CIC in men and women at a dosage of 24 μg twice daily. Lubiprostone is FDA-approved for the treatment of women with IBS-C at a dosage of 8 μg twice daily.

Summary of the evidence. No new RCTs of lubiprostone for the management of IBS-C were identified since the 2014 TR.[16] As reported previously, we identified 2 identically designed phase 3 RCTs that included 1154 patients with IBS-C.[58] Lubiprostone was superior to placebo for a modified FDA response (ie, adequate abdominal pain and SBM response; RR, 0.88; 95% CI, 0.79–0.96), adequate global response (RR, 0.93; 95% CI, 0.87–0.96), and abdominal pain relief (RR, 0.85; 95% CI, 0.76–0.95), but not SBM frequency (RR, 0.90; 95% CI, 0.75–1.10). With respect to adverse events leading to treatment discontinuation, a similar number of patients withdrew in the lubiprostone group (12.8%) vs placebo (12.3%). Adverse events specifically related to the gastrointestinal tract were reported in 19% of patients receiving lubiprostone compared with 14% receiving placebo. The overall certainty in evidence was MODERATE.

Rationale. Although there was a significantly beneficial effect of lubiprostone on global outcomes and abdominal pain response compared with placebo, these differences did not meet the threshold for being clinically meaningful. Furthermore, lubiprostone was not superior to placebo for adequate SBM response. It is not known whether lubiprostone would be associated with an improvement in CSBM response because CSBM was not measured. Data from a long-term safety extension study in patients with IBS-C found lubiprostone to be well tolerated for up to 13 months of treatment.[43]

6. Should Polyethylene Glycol Laxatives Be Used in Patients With Irritable Bowel Syndrome With Constipation?

The AGA suggests using PEG laxatives in patients with IBS-C.
(Conditional recommendation, low certainty in the evidence of effects)

This recommendation is unchanged from the 2014 IBS guideline.[17] PEG is a long-chain polymer of ethylene oxide,

which acts as an osmotic laxative. PEG without electrolytes is widely available for the treatment of constipation, including in the United States, where it is available over the counter.

Summary of the evidence. No new studies of PEG for the treatment of IBS-C were identified since the 2014 TR,[16] which included only 1 placebo-controlled trial.[59] This trial was a 4-week RCT that compared the efficacy of PEG 3350 in combination with electrolytes (PEG-E, n = 68) or placebo (13.8 sucrose with 0.1 g lemon and lime flavor, n = 71). Responders were defined as patients with pain reduction of >30%, >3 SBMs per week, and an increase of 1 SBM per week. In a post-hoc analysis, PEG-E was not associated with symptom relief based on the responder definition (RR, 0.90; 95% CI, 0.66–1.2) or abdominal pain response (RR, 0.93; 95% CI, 0.67–1.4). Other important outcomes, including CSBM responders, IBS-QOL, and adverse outcomes were not assessed or not reported. However, there was a significant improvement in SBM frequency with PEG compared with placebo. Additional limitations of this study included that it was a single-center study with a relatively short duration of treatment for an IBS clinical trial and used varying treatment doses per patient. The overall certainty in evidence for PEG laxatives was LOW.

Rationale. In clinical practice, PEG is commonly used for occasional constipation, CIC, and IBS-C. It has been shown to be efficacious in chronic constipation[60]; however, its effects on symptoms of IBS have not been well studied. Chapman et al[59] did not show a statistically significant or clinically meaningful improvement in abdominal pain or in the modified FDA responder end point for IBS-C in patients receiving PEG-E compared with placebo. Although this study showed a statistically significant improvement of CSBM frequency with PEG-E compared with placebo, the response rates could not be calculated on the basis of the available data. A more comprehensive assessment of PEG's efficacy in IBS-C could not be obtained due to having only 1 RCT that was composed of a relatively small number of patients compared with multicenter RCTs.

Although PEG has been shown to improve symptoms of constipation, larger high-quality studies are clearly needed to adequately evaluate the efficacy of PEG in patients with IBS-C in whom abdominal pain is a more predominant symptom.

7. Should Tricyclic Antidepressants Be Used in Patients With Irritable Bowel Syndrome?

The AGA suggests using TCAs in patients with IBS.
(Conditional recommendation, low certainty)

This recommendation is unchanged from the 2014 IBS guideline.[17] TCAs have been used to treat IBS symptoms due to their peripheral and central (ie, supraspinal and spinal) actions, which can affect motility, secretion, and sensation. IBS and other functional gastrointestinal disorders have been redefined in Rome IV as disorders of gut–brain interactions, characterized by any combination of motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous system processing.[61] Consistent with this redefinition and based on the fact that TCAs and other antidepressants have physiologic effects separate from the effect on mood, these agents have been relabeled as gut–brain neuromodulators.[62]

Summary of the evidence. The efficacy of TCAs in IBS was previously evaluated in the prior TR[16] based on 8 placebo-controlled RCTs in 523 patients (TCAs, n = 297; placebo, n = 226).[16] All but 1 study enrolled multiple IBS bowel habit subtypes. The type of TCA studied included amitriptyline (n = 3), desipramine (n = 2), trimipramine (n = 1), imipramine (n = 1), and doxepin (n = 1). The dose of the TCA varied from 10 mg to up to 150 mg and most studies used >50 mg per day. Global assessments differed among the trials and abdominal pain response was assessed in 4 trials. Compared with placebo, TCAs were associated with global symptom relief (RR, 0.67; 95% CI, 0.54–0.82) and abdominal pain relief (RR, 0.76–0.94). However, the quality of evidence was rated down due to indirectness, risk of bias, and imprecision. Based on data from 22 clinical trials in depression (as long-term high-quality data on adverse events with TCAs in IBS were not available), TCAs showed a significantly higher rate of withdrawals due to adverse effects compared with placebo (RR, 2.11; 95% CI, 1.35–3.28). The overall certainty in evidence for TCAs was LOW.

Rationale. TCAs were associated with greater responses of adequate relief and abdominal pain relief compared with placebo; however, only global relief response met the threshold for being clinically meaningful. The beneficial effects of TCAs on IBS symptoms appear to be independent of effects on depression and may take several weeks. Most studies evaluated higher doses of TCAs (ie, 50 mg and higher) than those used in clinical practice. There was 1 study demonstrating that amitriptyline 10 mg at bedtime had greater efficacy that placebo in patients with IBS-D.[63] TCAs have multiple actions, including inhibition of serotonin and noradrenergic reuptake and blockade of muscarinic 1, α1 adrenergic, and histamine 1 receptors.[62] These effects are beneficial (eg, reduce diarrhea and abdominal pain), but can also cause adverse events (eg, dry mouth, sedation, and constipation). Therefore, the selection of TCA should be based on the patient's symptom presentation. For example, secondary amine TCAs (eg, desipramine and nortriptyline) may be better tolerated in patients with IBS-C due to their lower anticholinergic effects.

8. Should Selective Serotonin Reuptake Inhibitors Be Used in Patients With Irritable Bowel Syndrome?

The AGA suggests against using SSRIs in patients with IBS.
(Conditional recommendation, low certainty)

This recommendation is unchanged from the 2014 IBS guideline.[17] SSRIs are approved for the treatment of mood disorders, such as anxiety and depression, but are also used in clinical practice to treat chronic pain conditions. SSRIs selectively inhibit the reuptake of 5-HT at presynaptic nerve endings, which results in an increased synaptic concentration of 5-HT. The use of SSRIs in IBS has been of considerable interest because IBS is considered a gut–brain disorder and these agents have centrally mediated effects and increase gastric and intestinal motility, although they do not appear to have a major impact on visceral sensation.[62]

Summary of the evidence. The efficacy of SSRIs in IBS was studied in 7 RCTs,[56,63–68] Most of the studies enrolled a mixture of all 3 main bowel habit subtypes. Patients with current psychiatric disease were generally excluded. Duration of treatment ranged from 6 weeks to 12 weeks. Different SSRIs were evaluated: fluoxetine 20 mg daily,[63,64] paroxetine 10 mg daily that could be increased,[67] paroxetine-CR 12.5–50 mg daily,[66] and 3 studies used citalopram at a starting dose of 20 mg, which was increased to 40 mg daily after 2,[68] 3,[56] or 4 weeks. Compared with placebo, SSRIs showed possible improvement in symptom relief (RR, 0.74; 95% CI, 0.52–1.06) and in abdominal pain or discomfort; however, the upper boundary of the CI suggested worsening symptoms of global relief or abdominal pain. The certainty in evidence for this outcome was rated as low due to serious inconsistency and imprecision. Two studies compared changes in IBS-specific QOL between the SSRI and placebo groups.[65,67] One study found a significantly greater improvement in food avoidance score[67] and the other study did not detect any differences.[65] The other critical or important outcomes could not be assessed based on the available data. There were no long-term data with SSRIs in IBS or depression to assess adverse events leading to treatment withdrawal.

Rationale. SSRIs did not significantly improve global symptoms or abdominal pain in IBS, although the overall certainty in evidence is low. Multiple factors, including those arising from central and peripheral processes, contribute to the severity of IBS symptoms. In some patients, SSRIs may improve the perception of overall IBS symptoms and well-being by improving gastrointestinal symptoms, coexistent alterations in mood and extraintestinal symptoms.[69] It is possible that serotonin-norepinephrine reuptake inhibitors may have a greater effect on abdominal pain in IBS due to their effects on both serotonin and norepinephrine reuptake. Serotonin-norepinephrine reuptake inhibitors have been shown to be efficacious in other pain conditions, but clinical trials in IBS are lacking.[62]

9. Should Antispasmodics Be Used in Patients With Irritable Bowel Syndrome?

The AGA suggests using antispasmodics in patients with IBS.
(Conditional recommendation, low certainty)

This recommendation is unchanged from the 2014 IBS guideline.[17] Antispasmodics are commonly used in clinical practice to reduce abdominal pain associated with IBS. Although a pharmacologically diverse class, antispasmodics are thought to relieve IBS symptoms by reducing smooth muscle contraction and possibly visceral hypersensitivity.[70] Of the antispasmodics studied, only hyoscine, dicyclomine, and peppermint oil are available in the United States.

Summary of evidence. This was based on a Cochrane Review that included 22 RCTs evaluating 2983 patients with IBS (antispasmodics n = 1008; placebo n = 1975).[71] Twelve different antispasmodics were assessed. There was considerable variation between the studies concerning diagnostic and inclusion criteria, dosing schedule, and study end points. Compared with placebo, there were a significantly greater proportion of patients taking antispasmodics who had adequate global relief of IBS symptoms (RR, 0.67; 95% CI, 0.55–0.80). The overall certainty in evidence, however, was low due to the serious risk of bias and publication bias. Likewise, compared with placebo, antispasmodics showed improvement in abdominal pain (RR, 0.74; 95% CI, 0.59–0.93). For this outcome, the certainty in evidence was very low due to risk of bias, publication bias, and imprecision (the upper boundary of the CI did not cross our minimal clinically important threshold). The effect of individual antispasmodics was difficult to interpret due to the small number of studies evaluated for each of the drugs. The most common adverse events reported were dry mouth, dizziness, and blurred vision, but no SAEs were reported. We did not include adverse events leading to discontinuation due to the lack of consistent reporting.

Rationale. Antispasmodics include a wide array of pharmacological therapies that been used clinically for many years but have not been subjected to rigorous large multicenter trials. There was considerable variation among the trials and the quality of the studies was generally low. However, antispasmodics were significantly associated with a greater relief of global symptoms and abdominal pain, although the latter did not meet our criteria for being clinically meaningful. A Cochrane Review[71] found a beneficial effect for antispasmodics over placebo for improvement in abdominal pain and global assessment. It is not clear whether antispasmodics are more efficacious in specific IBS subtypes, but their regular use in constipation may be limited due to its anticholinergic effects. Although these medications are often recommended for treatment of postprandial symptoms in IBS, this has not been studied specifically in RCTs.

Limitations and Evidence Gaps

A continued unmet need in IBS clinical trials is the lack of a biomarker that can embody the different pathophysiologic mechanisms of IBS or that can reliably predict treatment response to medications that have different predominant mechanisms of action (eg, normalizing bowel habits and visceral analgesic) and a need for clinically effective treatments that relieve multiple symptoms.

Dietary modification and behavioral treatments have shown beneficial effects in patients with IBS and should be considered on an individual basis, as these may be used in conjunction with pharmacological therapies. The efficacy of these interventions alone or in conjunction with pharmacological therapies was outside the scope this guideline. A recent AGA guideline on probiotics highlighted the evidence gaps in the use of probiotics in patients with IBS, and concluded that future, larger, and high-quality studies are needed.[72] In addition, studies evaluating the synergistic effects of combined treatment in IBS, which is often used in patients with moderate to severe symptoms in clinical practice, and better comparative effectiveness studies in IBS are needed.

Additional considerations related to the diagnostic criteria for IBS and use of specific outcomes are outlined below.

In 2016, the Rome IV diagnostic criteria for IBS were published, which differs from the Rome III criteria[42] in that abdominal discomfort has been deleted from the definition and abdominal pain now is required to be present at least 1 day per week on average during the preceding 3 months.[27] Based on these changes, fewer individuals meet the Rome IV criteria for IBS compared with the Rome III criteria.[73] However, for the purpose of RCTs in IBS, which generally measure changes in abdominal pain, the Rome IV criteria are more applicable. However, it is conceivable that the Rome III–positive study populations that qualified for enrollment into RCTs had symptoms that also met Rome IV criteria because a certain level of baseline symptom severity is required to show a symptom benefit.[74] Nonetheless, it is not known whether these changes to the IBS diagnostic criteria would alter the efficacy and safety of IBS treatments in RCTs.

- Responder definitions have varied in multicenter IBS RCTs until the establishment of FDA composite primary end points for IBS-C in 2012,[29] which now allows greater standardization of the efficacy of IBS treatments than in the past. However, these end points were meant to serve as interim primary end points while a patient-reported outcome instrument was being developed as recommended by the FDA guidance for patient-reported outcome.[75] An FDA-approved IBS patient-reported outcome for IBS-C was completed recently.[76] The FDA recommended enrollment criteria and interim primary end points for IBS-C but not IBS-mixed type. There continues to be a lack of studies focusing on IBS-mixed type and no consensus on the optimal primary end point for this bowel habit subgroup. With respect to therapeutic agents that target abdominal pain relief without significant effects on bowel habits, there is no established consensus on the inclusion and exclusion criteria regarding bowel symptoms and treatment that normalizes bowel habits without an effect on abdominal pain (eg, antidiarrheals and laxatives).

Implementation, Cost, and Health Equity Considerations

This guideline is helpful in outlining the various pharmacotherapeutic agents recommended for use in managing symptoms of IBS-C. Acknowledging that multimodal treatments that include dietary and behavioral approaches in conjunction with drug therapy may provide maximal benefits and that treatment choices may be influenced by patient preferences, practitioners should engage in shared decision making with patients when choosing the best therapy. The importance of the patient–physician relationship is paramount in caring for individuals with IBS. Most drugs for the treatment of IBS-C are readily available and covered by prescription drug plans, yet newer drugs are still only available in brand name formulations as generic formulations do not yet exist. Out-of-pocket expenses for patients can vary widely, depending on prescription coverage with various insurance plans and this is an important factor to consider when choosing between different options. Some patient-assistance programs exist that can offset drug costs. Prior authorizations may be required by some insurance companies, and the case for prescribing is strengthened when a patient has tried and failed generic therapies. The Guideline, clinical decision support tool, and infographic are available on the AGA website (www.gastro.org).

Plans for Updating This Guideline

Guidelines need to be updated regularly to remain useful. Keeping guidelines up to date is a challenging process. Future advances in technological platforms and models of guideline development incorporating living reviews and living guidelines will hopefully provide opportunities for more agile and rapid updates to recommendations and as new evidence emerges and as new interventions are studied, without duplication and reproduction of full guideline documents.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dxdoi.org/10.1053/j.gastro.2022.04.016.

References

1. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. Clin Gastroenterol Hepatol 2012;10:712–721.e4.
2. Palsson OS, Whitehead W, Tornblom H, et al. Prevalence of Rome IV functional bowel disorders among adults in the United States, Canada, and the United Kingdom. Gastroenterology 2020;158:1262–1273.e3.
3. Sperber AD, Bangdiwala SI, Drossman DA, et al. Worldwide prevalence and burden of functional gastrointestinal disorders, results of Rome Foundation Global Study. Gastroenterology 2021;160:99–114.e3.

4. Monnikes H. Quality of life in patients with irritable bowel syndrome. J Clin Gastroenterol 2011;45(Suppl): S98–S101.
5. Lea R, Whorwell PJ. Quality of life in irritable bowel syndrome. Pharmacoeconomics 2001;19:643–653.
6. Singh P, Agnihotri A, Pathak MK, et al. Psychiatric, somatic and other functional gastrointestinal disorders in patients with irritable bowel syndrome at a tertiary care center. J Neurogastroenterol Motil 2012;18:324–331.
7. Nellesen D, Yee K, Chawla A, et al. A systematic review of the economic and humanistic burden of illness in irritable bowel syndrome and chronic constipation. J Manag Care Pharm 2013;19:755–764.
8. Singh P, Staller K, Barshop K, et al. Patients with irritable bowel syndrome-diarrhea have lower disease-specific quality of life than irritable bowel syndrome-constipation. World J Gastroenterol 2015;21:8103–8109.
9. Drossman DA, Li Z, Andruzzi E, et al. U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. Dig Dis Sci 1993;38:1569–1580.
10. Frandemark A, Tornblom H, Jakobsson S, et al. Work productivity and activity impairment in irritable bowel syndrome (IBS): a multifaceted problem. Am J Gastroenterol 2018;113:1540–1549.
11. Pare P, Gray J, Lam S, et al. Health-related quality of life, work productivity, and health care resource utilization of subjects with irritable bowel syndrome: baseline results from LOGIC (Longitudinal Outcomes Study of Gastrointestinal Symptoms in Canada), a naturalistic study. Clin Ther 2006;28:1726–1735; discussion 1710–1711.
12. Hungin AP, Whorwell PJ, Tack J, et al. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. Aliment Pharmacol Ther 2003;17:643–650.
13. Hungin AP, Chang L, Locke GR, et al. Irritable bowel syndrome in the United States: prevalence, symptom patterns and impact. Aliment Pharmacol Ther 2005; 21:1365–1375.
14. Ballou S, McMahon C, Lee HN, et al. Effects of irritable bowel syndrome on daily activities vary among subtypes based on results from the IBS in America survey. Clin Gastroenterol Hepatol 2019;17:2471–2478.e3.
15. Kellow JE, Drossman DA, Chang L, et al, eds. Rome IV Diagnostic Algorithms for Common GI Symptoms. 2nd ed. Rome Foundation, 2016.
16. Chang L, Lembo A, Sultan S. American Gastroenterological Association Institute Technical Review on the pharmacological management of irritable bowel syndrome. Gastroenterology 2014;147:1149–1172.e2.
17. Weinberg DS, Smalley W, Heidelbaugh JJ, et al. American Gastroenterological Association Institute guideline on the pharmacological management of irritable bowel syndrome. Gastroenterology 2014;147:1146–1148.
18. Sultan S, Falck-Ytter Y, Inadomi JM. The AGA Institute process for developing clinical practice guidelines part one: grading the evidence. Clin Gastroenterol Hepatol 2013;11:329–332.
19. Drossman D, Morris CB, Hu Y, et al. Characterization of health related quality of life (HRQOL) for patients with functional bowel disorder (FBD) and its response to treatment. Am J Gastroenterol 2007;102:1442–1453.
20. Higgins JPT, Greene S, eds. Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0. The Cochrane Collaboration, 2011.
21. Brozek J, Nowak A, Kuntsman P, et al. GRADEpro Guideline Development Tool. Evidence Prime, 2019. Available at: https://gradepro.org. Accessed April 19, 2022.
22. Spencer AG, Labonte ED, Rosenbaum DP, et al. Intestinal inhibition of the Na+/H+ exchanger 3 prevents cardiorenal damage in rats and inhibits Na+ uptake in humans. Sci Transl Med 2014;6:227ra36.
23. Eutamene H, Charmot D, Navre M, et al. Visceral antinociceptive effects of RDX5791, a first-in-class minimally systemic NHE3 inhibitor on stress-induced colorectal hypersensitivity to distension in rats. Gastroenterology 2011;140:S-57–S-58.
24. Chey WD, Lembo AJ, Rosenbaum DP. Tenapanor treatment of patients with constipation-predominant irritable bowel syndrome: a phase 2, randomized, placebo-controlled efficacy and safety trial. Am J Gastroenterol 2017;112:763–774.
25. Chey WD, Lembo AJ, Rosenbaum DP. Efficacy of tenapanor in treating patients with irritable bowel syndrome with constipation: a 12-week, placebo-controlled phase 3 trial (T3MPO-1). Am J Gastroenterol 2020;115:281–293.
26. Chey WD, Lembo AJ, Yang Y, et al. Efficacy of tenapanor in treating patients with irritable bowel syndrome with constipation: a 26-week, placebo-controlled phase 3 trial (T3MPO-2). Am J Gastroenterol 2021;116:1294–1303.
27. Mearin F, Lacy BE, Chang L, et al. Bowel disorders. Gastroenterology 2016;150:1393–1407.
28. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol 1997; 32:920–924.
29. Guidance for Industry, Irritable Bowel Syndrome - Clinical Evaluation of Drug for Treatment; Availability. US Food and Drug Administration. Federal Register. Published May 31, 2012. Available at: https://www.federalregister.gov/documents/2012/05/31/2012-13143/guidance-for-industry-on-irritable-bowel-syndrome-clinical-evaluation-of-drugs-for-treatment. Accessed April 19, 2022.
30. Brancale A, Shailubhai K, Ferla S, et al. Therapeutically targeting guanylate cyclase-C: computational modeling of plecanatide, a uroguanylin analog. Pharmacol Res Perspect 2017;5:e00295.
31. Boulete IM, Thadi A, Beaufrand C, et al. Oral treatment with plecanatide or dolcanatide attenuates visceral hypersensitivity via activation of guanylate cyclase-C in rat models. World J Gastroenterol 2018;24:1888–1900.
32. Brenner DM, Fogel R, Dorn SD, et al. Efficacy, safety, and tolerability of plecanatide in patients with irritable bowel syndrome with constipation: results of two phase 3 randomized clinical trials. Am J Gastroenterol 2018; 113:735–745.
33. Miner P, DeLuca R, La Portilla M, et al. Plecanatide, a novel uroguanylin analog: a 12-week, randomized, double-blind, placebo-controlled, dose-ranging trial to evaluate efficacy and safety in patients with irritable

bowel syndrome with constipation (IBS-C). Am J Gastroenterol 2014:S541.
34. Shah ED, Kim HM, Schoenfeld P. Efficacy and tolerability of guanylate cyclase-C agonists for irritable bowel syndrome with constipation and chronic idiopathic constipation: a systematic review and meta-analysis. Am J Gastroenterol 2018;113:329–338.
35. Silos-Santiago I, Hannig G, Eutamene H, et al. Gastrointestinal pain: unraveling a novel endogenous pathway through uroguanylin/guanylate cyclase-C/cGMP activation. Pain 2013;154:1820–1830.
36. Hannig G, Tchernychev B, Kurtz CB, et al. Guanylate cyclase-C/cGMP: an emerging pathway in the regulation of visceral pain. Front Mol Neurosci 2014;7:31.
37. Castro J, Harrington AM, Hughes PA, et al. Linaclotide inhibits colonic nociceptors and relieves abdominal pain via guanylate cyclase-C and extracellular cyclic guanosine 3',5'-monophosphate. Gastroenterology 2013; 145:1334–1346; e1–e11.
38. Rao S, Lembo AJ, Shiff SJ, et al. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. Am J Gastroenterol 2012;107:1714–1724; quiz 1725.
39. Johnston JM, Kurtz CB, Macdougall JE, et al. Linaclotide improves abdominal pain and bowel habits in a phase IIb study of patients with irritable bowel syndrome with constipation. Gastroenterology 2010;139: 1877–1886.e2.
40. Chey WD, Lembo AJ, Lavins BJ, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. Am J Gastroenterol 2012; 107:1702–1712.
41. Yang Y, Fang J, Guo X, et al. Linaclotide in irritable bowel syndrome with constipation: A Phase 3 randomized trial in China and other regions. J Gastroenterol Hepatol 2018;33:980–989.
42. Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. Gastroenterology 2006; 130:1480–1491.
43. Chey WD, Drossman DA, Johanson JF, et al. Safety and patient outcomes with lubiprostone for up to 52 weeks in patients with irritable bowel syndrome with constipation. Aliment Pharmacol Ther 2012;35:587–599.
44. Black CJ, Burr NE, Quigley EMM, et al. Efficacy of secretagogues in patients with irritable bowel syndrome with constipation: systematic review and network meta-analysis. Gastroenterology 2018;155:1753–1763.
45. Tack J, Camilleri M, Chang L, et al. Systematic review: cardiovascular safety profile of 5-HT(4) agonists developed for gastrointestinal disorders. Aliment Pharmacol Ther 2012;35:745–767.
46. Anderson JL, May HT, Bair TL, et al. Lack of association of tegaserod with adverse cardiovascular outcomes in a matched case-control study. J Cardiovasc Pharmacol Ther 2009;14:170–175.
47. Loughlin J, Quinn S, Rivero E, et al. Tegaserod and the risk of cardiovascular ischemic events: an observational cohort study. J Cardiovasc Pharmacol Ther 2010; 15:151–157.
48. Shah ED, Lacy BE, Chey WD, et al. Tegaserod for irritable bowel syndrome with constipation in women younger than 65 years without cardiovascular disease: pooled analyses of 4 controlled trials. Am J Gastroenterol 2021;116:1601–1611.
49. Muller-Lissner SA, Fumagalli I, Bardhan KD, et al. Tegaserod, a 5-HT(4) receptor partial agonist, relieves symptoms in irritable bowel syndrome patients with abdominal pain, bloating and constipation. Aliment Pharmacol Ther 2001;15:1655–1666.
50. Lefkowitz M, Shi Y, Schmitt C, et al. The 5-HT4 partial agonist, tegaserod, improves abdominal discomfort/pain and normalizes altered bowel function in irritable bowel syndrome (IBS). Am J Gastroenterol 1999;94:266.
51. Novick J, Miner P, Krause R, et al. A randomized, double-blind, placebo-controlled trial of tegaserod in female patients suffering from irritable bowel syndrome with constipation. Aliment Pharmacol Ther 2002; 16:1877–1888.
52. US Food and Drug Administration. FDA Briefing Document: Joint Meeting of the Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committees. Published October 17, 2018. Available at: https://www.fda.gov/media/119011/download. Accessed April 19, 2022.
53. Layer P, Keller J, Loeffler H, et al. Tegaserod in the treatment of irritable bowel syndrome (IBS) with constipation as the prime symptom. Ther Clin Risk Manag 2007;3:107–118.
54. Kellow J, Lee OY, Chang FY, et al. An Asia-Pacific, double blind, placebo controlled, randomised study to evaluate the efficacy, safety, and tolerability of tegaserod in patients with irritable bowel syndrome. Gut 2003; 52:671–676.
55. Nyhlin H, Bang C, Elsborg L, et al. A double-blind, placebo-controlled, randomized study to evaluate the efficacy, safety and tolerability of tegaserod in patients with irritable bowel syndrome. Scand J Gastroenterol 2004;39:119–126.
56. Tack J, Broekaert D, Fischler B, et al. A controlled crossover study of the selective serotonin reuptake inhibitor citalopram in irritable bowel syndrome. Gut 2006; 55:1095–1103.
57. Camilleri M, Bharucha AE, Ueno R, et al. Effect of a selective chloride channel activator, lubiprostone, on gastrointestinal transit, gastric sensory, and motor functions in healthy volunteers. Am J Physiol Gastrointest Liver Physiol 2006;290:G942–G947.
58. Drossman DA, Chey WD, Johanson JF, et al. Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome—results of two randomized, placebo-controlled studies. Aliment Pharmacol Ther 2009;29:329–341.
59. Chapman RW, Stanghellini V, Geraint M, et al. Randomized clinical trial: macrogol/PEG 3350 plus electrolytes for treatment of patients with constipation associated with irritable bowel syndrome. Am J Gastroenterol 2013;108:1508–1515.

60. Ford AC, Moayyedi P, Lacy BE, et al. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. Am J Gastroenterol 2014;109(Suppl 1):S2–S26; quiz S27.
61. Drossman DA, Hasler WL. Rome IV-functional GI disorders: disorders of gut-brain interaction. Gastroenterology 2016;150:1257–1261.
62. Drossman DA, Tack J, Ford AC, et al. Neuromodulators for functional gastrointestinal disorders (disorders of gut-brain interaction): a rome foundation working team report. Gastroenterology 2018; 154:1140–1171.e1.
63. Vahedi H, Merat S, Momtahen S, et al. Clinical trial: the effect of amitriptyline in patients with diarrhoea-predominant irritable bowel syndrome. Aliment Pharmacol Ther 2008;27:678–684.
64. Kuiken SD, Tytgat GN, Boeckxstaens GE. The selective serotonin reuptake inhibitor fluoxetine does not change rectal sensitivity and symptoms in patients with irritable bowel syndrome: a double blind, randomized, placebo-controlled study. Clin Gastroenterol Hepatol 2003; 1:219–228.
65. Ladabaum U, Sharabidze A, Levin TR, et al. Citalopram provides little or no benefit in nondepressed patients with irritable bowel syndrome. Clin Gastroenterol Hepatol 2010;8:42–48.e1.
66. Masand PS, Pae CU, Krulewicz S, et al. A double-blind, randomized, placebo-controlled trial of paroxetine controlled-release in irritable bowel syndrome. Psychosomatics 2009;50:78–86.
67. Tabas G, Beaves M, Wang J, et al. Paroxetine to treat irritable bowel syndrome not responding to high-fiber diet: a double-blind, placebo-controlled trial. Am J Gastroenterol 2004;99:914–920.
68. Talley NJ, Kellow JE, Boyce P, et al. Antidepressant therapy (imipramine and citalopram) for irritable bowel syndrome: a double-blind, randomized, placebo-controlled trial. Dig Dis Sci 2008;53: 108–115.
69. Grover M, Drossman DA. Psychotropic agents in functional gastrointestinal disorders. Curr Opin Pharmacol 2008;8:715–723.
70. Khalif IL, Quigley EM, Makarchuk PA, et al. Interactions between symptoms and motor and visceral sensory responses of irritable bowel syndrome patients to spasmolytics (antispasmodics). J Gastrointestin Liver Dis 2009;18:17–22.
71. Ruepert L, Quartero AO, de Wit NJ, et al. Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. Cochrane Database Syst Rev 2011:CD003460.
72. Su GL, Ko CW, Bercik P, et al. AGA Clinical Practice Guidelines on the role of probiotics in the management of gastrointestinal disorders. Gastroenterology 2020; 159:697–705.
73. Palsson OS, Whitehead WE, van Tilburg MA, et al. Rome IV diagnostic questionnaires and tables for investigators and clinicians. Gastroenterology 2016;150:1481–1491.
74. Shin A, Chang L. The transition from Rome III to Rome IV irritable bowel syndrome: what we gain and lose. Clin Gastroenterol Hepatol 2022;20:508–510.
75. US Food and Drug Administration. Guidance for Industry, Patient Reported Outcomes: Use in Medical Product Development to Support Labeling Claims; Availability. Published December 9, 2019. Available at: https://www.federalregister.gov/documents/2009/12/09/E9-29273/guidance-for-industry-on-patient-reported-outcome-measures-use-in-medical-product-development-to. Accessed April 19, 2022.
76. Fehnel SE, Ervin CM, Carson RT, et al. Development of the diary for irritable bowel syndrome symptoms to assess treatment benefit in clinical trials: foundational qualitative research. Value Health 2017;20:618–626.

Correspondence
Address correspondence to: Chair, Clinical Guidelines Committee, American Gastroenterological Association, National Office, 4930 Del Ray Avenue, Bethesda, Maryland 20814. e-mail: clinicalpractice@gastro.org.

Acknowledgments
The authors sincerely thank Kellee Kaulback, Medical Information Officer, for helping in the literature search for the evidence review.

Conflicts of interest
These authors disclose the following: Lin Chang has served as a member of the scientific advisory boards for Ardelyx, Immunic, Ironwood Mauna Kea Technologies, and Protagonist. She has served as a consultant for Trellus and a speaker for Abbvie. She has received research support from the National Institute of Health, Arena, AnX Robotica, and Ironwood. She has stock options with ModifyHealth and Trellus. Anthony Lembo has served as a member of the scientific advisory board for Arena, Ardelyx, Bioamerica, IM HealthSciences, Mauno Kea Technologies, Ironwood, Mylan, Orpho-Med, Ritter, Shire, Takeda, Vibrant and Allergan. He has received research support for clinical trials from National Institute of Health, Arena, Takeda, Vanda, and Vibrant, and Vanda. The remaining authors disclose no conflicts.

Funding
G. Nicholas Verne is supported by the National Institute of Diabetes and Digestive and Kidney Diseases (DK099052 and DK118959). Shahnaz Sultan is supported by the National Heart, Lung, and Blood Institute at the National Institute of Health for Asthma Guideline Development.